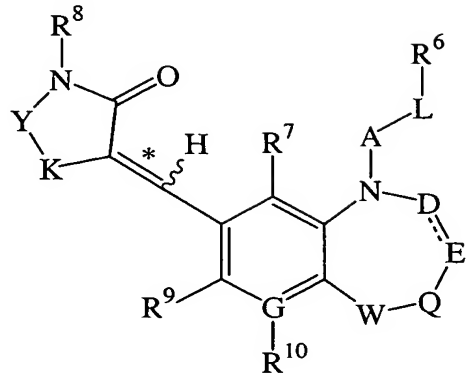
CLAIMS

What is claimed is:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof;

or a pharmaceutically acceptable salt thereof;

wherein W is O, S, or NR^{21};

wherein R^{21} is selected from the group consisting of:–H, $-CF_3$, a C_{1-6}alkyl, and phenyl;

wherein Q is $(CR^2R^3)_p$,

wherein R^2 and R^3 are independently selected from H or $-CH_3$;

wherein p is 0 or 1;

wherein E is CR^4R^5;

wherein R^4 and R^5 are independently selected from H or $-CH_3$;

wherein D is $CR^{28}R^{30}$;

wherein R^{28} and R^{30} are independently selected from H or $-CH_3$;

wherein the dashed bond between D and E can be absent or present;

wherein A is absent, $-S(O)_2-$, -C(O)-, -C(O)-O-, -C(O)-NH-, or -C(S)-NH-;

wherein L is absent, a C_1-C_3-alkylene, $-CH_2-$, $-(CH_2)_2-$, -CH=CH-, a C_2-C_3-alkenylene, $-CH_2-O-$, $-C_1$-C_3-alkyl-O-, $-CH_2-O-CH_2-$, $-C_1$-C_3-alkyl-O-C_1-C_3-alkyl, $-CH_2-S-$, $-C_1$-C_3-alkyl-S-, C_1-C_3-alkyl-S(O)-, C_1-C_3-alkyl-$S(O)_2-$, $-C_1$-C_3-alkyl-S-C_1-C_3-alkyl-, - C_1-C_3alkyl-CO-, - C_1-C_3alkyl-C(O)O-, $-C_1$-C_3alkyl-C(O)-CH_2-, $-C_1$-C_3alkyl-

$C(O)NR^{22}$-, -C_1-C_3alkyl-NR^{22}-C(O)-, -C_1-C_3alkyl-NR^{22}-C(O)-NR^{24}-, or -C_1-C_3alkyl-NR^{22}-;

wherein R^{22} and R^{24} are independently selected from H, and C_{1-3}alkyl;

wherein R^6 is selected from the group consisting of H, a C_{1-9}alkyl, a C_{2-9}alkenyl, a C_{2-9}alkynyl, $C(C_1$-C_5alkyl$)(C_1$-C_5alkyl), a C_3-C_8cycloalkyl, a 3- to 8-membered heterocycloalkyl, a piperidinyl, a 6- to 12-membered bicyclic heterocycloalkyl, a 6- to 11-membered bridged bicyclic heterocycloalkyl, a 5-membered heteroaryl, a 5-isoxazolyl, a 3-isoxazolyl, an isoxazolyl, a 2-furanyl, a 3-furanyl, a 2-thienyl, a 3-thienyl, a thienyl, a 6-membered heteroaryl, a pyridinyl, a 4-pyridinyl, a 3-pyridinyl, an 8-to 12-membered bicyclic heteroaryl, a 2-quinoxalinyl, a quinoxalinyl, a phenyl, a naphthalenyl, a 1-naphthalenyl, a 2-naphthalenyl, a 9- to 12-membered bicyclic aryl, a 9,10-dioxo-9,10-dihydro-anthracen-2-yl, a benzofurazanyl, and a 4-(2,2-difluoro-1,3-benzodioxolyl;

wherein R^7 is H, F, CF_3, or CH_3;

wherein R^8 is H, $–CH_2COOH$, phenyl, $-CH_3$, a C_{1-6}alkyl, or a C_{2-6}alkenyl;

wherein Y is C(O), or C(S);

wherein K is NH, O, CH_2, or S;

wherein R^9 is H, F, CF_3, or CH_3;

wherein G is C-R^{10} or N;

wherein R^{10} is H, -O-C_{1-3}alkyl, a C_{1-3}alkyl, $-NO_2$, -$NR^{16}R^{18}$, a -S-C_{1-3}alkyl, F or Cl;

wherein R^{16} and R^{18} are independently selected from the group consisting of: H, and C_{1-3}alkyl; and

wherein the stereochemistry of the double bond denoted "*" is entgegen or zusammen.

2. The compound of claim 1, wherein K is S, Y is C(S), and R^8 is H.

3. The compound of claim 2, wherein W is O, G is C-R^{10}, p is 0, and R^4, R^5, R^7, R^8, R^9, R^{10}, $R^{28}$and R^{30} are H; and wherein the dashed bond between D and E is absent.

4. The compound of claim 1, wherein R^6 is selected from the group consisting of H, a C_{1-9}alkyl, a C_{2-9}alkenyl, a C_{2-9}alkynyl, C(C_1-C_5alkyl)(C_1-C_5alkyl), a C_3-C_8cycloalkyl, a phenyl, a naphthalenyl, a 1-naphthalenyl, and a 2-naphthalenyl.

5. The compound of claim 1, wherein L is absent, a C_1-C_3-alkylene, -CH_2-, -$(CH_2)_2$-, -CH=CH-, a C_2-C_3-alkenylene, -CH_2-O-, -C_1-C_3-alkyl-O-, -CH_2-O-CH_2-, -C_1-C_3-alkyl-O-C_1-C_3-alkyl, -CH_2-S-, -C_1-C_3-alkyl-S-, or -C_1-C_3-alkyl-S-C_1-C_3-alkyl-.

6. The compound of claim 1, wherein A is -C(O)-, -C(O)-O-, or -C(O)-NH-.

7. The compound of claim 3, wherein R^6 is H, a C_{1-9}alkyl, a C_{2-9}alkenyl, a C_{2-9}alkynyl, C(C_1-C_5alkyl)(C_1-C_5alkyl), a C_3-C_8cycloalkyl, a phenyl, a naphthalenyl, a 1-naphthalenyl, or a 2-naphthalenyl.

8. The compound of claim 7, wherein L is absent, a C_1-C_3-alkylene, -CH_2-, -$(CH_2)_2$-, -CH=CH-, a C_2-C_3-alkenylene, -CH_2-O-, -C_1-C_3-alkyl-O-, -CH_2-O-CH_2-, -C_1-C_3-alkyl-O-C_1-C_3-alkyl-, -CH_2-S-, -C_1-C_3-alkyl-S-, or -C_1-C_3-alkyl-S-C_1-C_3-alkyl-.

9. The compound of claim 8, wherein R^6 is H, a C_{1-9}alkyl, a C_{2-9}alkenyl, a C_{2-9}alkynyl, or a C(C_1-C_3alkyl)(C_1-C_5alkyl).

10. The compound of claim 9, wherein the compound is selected from the group consisting of:

5-(4-Isobutyryl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-2-thioxo-thiazolidin-4-one;

5-(4-Heptanoyl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-2-thioxo-thiazolidin-4-one;

8-Oxo-8-[6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-yl]-octanoic acid methyl ester; and

5-(4-Pentanoyl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-2-thioxo-thiazolidin-4-one.

11. The compound of claim 8, wherein R^6 is a phenyl, a naphthalenyl, a 1-naphthalenyl, or a 2-naphthalenyl.

12. The compound of claim 9, wherein the compound is selected from the group consisting of:

4-[2-(3,4-Dichloro-phenyl)-acetyl]-3,4-dihydro-2H-benzo[1,4]oxazine-6-ylmethylene]-2-thioxo-thiazolidin-4-one;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid phenyl ester;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid p-tolyl ester;

5-[4-(3-Phenyl-acryloyl)-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-2-thioxo-thiazolidin-4-one;

5-[4-(2-Benzyloxy-acetyl)-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-2-thioxo-thiazolidin-4-one;

5-[4-(2-Phenylsulfanyl-acetyl)-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-2-thioxo-thiazolidin-4-one;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid 4-methoxycarbonyl-phenyl ester;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid (3-trifluoromethyl-phenyl)-amide;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid phenethyl-amide;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid naphthalen-1-yl ester;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid (4-chloro-phenyl)-amide;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid (3,4-dichloro-phenyl)-amide;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid (3,5-dimethyl-phenyl)-amide; and

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid (3-chloro-phenyl)-amide.

13. The compound of claim 8, wherein R^6 is a C_3-C_8cycloalkyl.

14. The compound of claim 13, wherein the compound is selected from the group consisting of:

5-[4-(3-Cyclopentyl-propionyl)-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-2-thioxo-thiazolidin-4-one;

6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylic acid cyclopentylamide; and

5-[4-(3-Methyl-cyclohexanecarbonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-ethylene]-2-thioxo-thiazolidin-4-one.

15. A method of treating a subject suffering from a PI3K-mediated disorder or condition comprising:

administering, to a subject suffering from a PI3K-mediated condition or disorder, a pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

16. The method of claim 15, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:

rheumatoid arthritis, osteoarthritis, inflammatory diseases, and autoimmune diseases.

17. The method of claim 15, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:

cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease.

18. The method of claim 15, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:

cancer, breast cancer, gliobastoma, endometrial carcinoma, heptocellular carcinoma, colon cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, leukemia, cell lymphoma, and lymphoproliferative disorders.

19. The method of claim 15, wherein said PI3K-mediated condition or disorder is selected from the group consisting of: type II diabetes.

20. The method of claim 15, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:

respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease.

21. The method of claim 15, wherein said compound is a compound of any one of claims 1-14.

22. A pharmaceutical composition comprising:

a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition comprising:

a therapeutically effective amount of a compound of claim 1-14 and a pharmaceutically acceptable carrier.